Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-61 are pending in the application, with 1, 19, 27, 38, 44, and 50 being the independent claims. Claims 56-61 are new. These changes are believed to introduce no new matter, and their entry is respectfully requested.

New claims 56-61 are directed to substantially pure compounds of the present invention. Support for these claims can be found throughout the application. These new claims do not introduce new matter.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and further request that they be withdrawn.

Description of the Invention

The present invention is directed to tamandarin or didemnin compounds, compositions comprising said compounds, and methods of using and making said compounds and compositions.

Restriction Requirement

Applicants thank the Examiner for his reconsideration and withdrawal of the previously pending restriction requirement. Applicants also thank the Examiner for acknowledgment of the Information Disclosure Statements filed on June 28, 2001, and July 17, 2001.

Objection to the Claims

The Examiner has objected to claims 3 and 29 for being duplicative of claims 2 and 28, respectively. Applicants respectfully disagree. While claim 3 may appear to be of similar scope as claim 2, claim 2 is actually broader in scope in certain aspects. Specifically, the stereochemistry of certain amino acid residues of R^1 is not specified in claim 2. For example, the fifth R^1 group recited in claim 2 is -(N-methyl)leucine-deoxo-(S)proline-(S)lactate-glutamine-pyroglutamate. In claim 3, the fifth R^1 group recited is -(N-methyl)leucine-deoxo-(S)proline-(S)lactate-(S)glutamine-(S)pyroglutamate (emphasis added). The R^1 group in claim 3 specifies that the glutamine and pyroglutamate residues have the *S* configuration, whereas, in claim 2, the configurations of the glutamine and pyroglutamate residues are unspecified, *i.e.*, they can be *S* or *R*. This difference is apparent for other residues in claims 2 and 3, and is likewise applicable to claims 28 and 29. However, to expedite prosecution, Applicants have removed R^1 groups from claims 3 and 29 that were repeated from claims 2 and 28, respectively.

The differences between claims 2 and 3 and between claims 28 and 29 are more than a difference in wording. The amended claims clearly have a different scope and are clearly not word for word duplicates. Applicants respectfully request reconsideration and withdrawal of the objection of claims 3 and 29.

Rejections under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 14-18, 22-26, and 39-43 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the

specification in such a way as to enable the invention as claimed. Applicants respectfully traverse the rejection.

The Examiner contends that the methods of claims 14-18, 22-26, and 39-43 are not enabled. These claims are directed to methods of inhibiting protein synthesis, cell growth, cell proliferation, and tumorigenesis, and of enhancing apoptosis. The Examiner states that "the specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims." The Examiner further states that "one of skill in the art would find that [an] undue amount of experimentation would be required to practice the full scope of the extremely broad claims . . . ." Applicants respectfully disagree.

Applicants describe their compounds and methods of making and using them in sufficient detail to allow one of ordinary skill in the art to make and use the compounds. Indeed, the Examiner has determined that the compound, composition, and method of making claims meet the requirements of 35 U.S.C. 112, paragraph 1. Applicants further provide an enabling description of the methods of claims 14-18, 22-26, and 39-43. Specifically, Applicants recited specific uses of the compounds, including dosages and subjects of treatment. See, *e.g.*, page 38 of the application.

As required by *In re Borkowski*, 164 U.S.P.Q. 642 (C.C.P.A. 1970), Applicants' invention is enabled. The application fully sets forth the necessary guidance to enable those of skill in the art to apply or administer the compounds and compositions so that the intended result occurs. The descriptions sufficiently demonstrate that Applicants' compounds would be accepted by those skilled in the art as being useful in the claimed

methods. Based on the specification, one of ordinary skill in the art would be able to prepare a composition useful in the claimed methods. Taken as a whole, it is seen that the supporting disclosure is commensurate in scope with the methods as claimed. As the Federal Circuit has recently noted,

> [t]he enablement requirement is often more indulgent than the written description requirement. The specification need not explicitly teach those in the art to make and use the invention; the requirement is satisfied if, given what they already know, the specification teaches those in the art enough that they can make and use the invention without "undue experimentation."

Amgen, Inc., v. Hoechst Marion Rousell, Inc., 65 U.S.P.Q.2d 1385, 1400 (Fed. Cir. 2003) (citations omitted).

To support the rejection, the Examiner cited Grubb *et al.*, "Didemnin B Induces Cell Death by Apoptosis: The Fastest Induction of Apoptosis Ever Described," *Biochem. Biophys. Res. Commun. 215*:1130-1136 (1995) ("Grubb"). The Examiner cited Grubb for the proposition that the mechanism by which didemnin B exerts its biological effects is obscure. Although Grubb does state that, with respect to precise details, the mechanism of didemnin B remains obscure, the article also clearly and explicitly teaches that didemnin B inhibits protein synthesis and has potent antineoplastic activity. Grubb at 1130. Inhibition of cell growth, cell proliferation, and tumorigenesis are all properties of a compound that one of ordinary skill in the art would associate with antineoplastic activity. Grubb also confirms that didemnin B induces apoptosis. *Id.* at 1131 ("[T]he mechanism of didemnin B's cytotoxicity in HL-60 cells is the induction of apoptosis."). Indeed, the title of Grubb clearly indicates that didemnin B induces apoptosis.

In view of the teaching of Grubb, it is the Applicants' respectful position that the Examiner has not met his burden of establishing a *prima facie* lack of enablement of claims 14-18, 22-26, and 39-43.

The Examiner also states that "the claims are based on pure speculation that the methods would be effective since Applicant[s] ha[ve] not established any *nexus* between the claimed composition and their use in the manner claimed." (Office Action, p. 8, (emphasis in original)). Applicants respectfully disagree that the claims are based on pure speculation. One of ordinary skill in the art would not expect that the compounds of the present invention would have significantly different properties compared to the known structurally similar didemnins and tamandarins. *See In re Brana*, 34 U.S.P.Q.2d 1437, 1441 (Fed. Cir. 1995). In fact, Grubb teaches that didemnins have the properties required of the claimed methods. Consistent with that knowledge, the claimed methods neither are inherently unbelievable nor involve an implausible scientific theory. *See In re Jolles*, 206 U.S.P.Q. 885, 890 (C.C.P.A. 1980). Thus, one of ordinary skill in the art would have no reason to think that the claimed methods, using didemnin and tamandarin analogs of the present invention, would not exert similar effects compared to the use of known didemnins or tamandarins.

Additionally, the Examiner considers the lack of data or examples as being indicative of a lack of enablement. For example, the Examiner states that "[t]here is no evidence in the instant specification to use or administer the various compositions in the manner claimed." (Office Action, p. 6). However, both the C.C.P.A. and the Federal Circuit have held that a working example is not required for a specification to be

enabling. *In re Strahilevitz*, 212 U.S.P.Q. 561 (C.C.P.A. 1982); *see also Spectra-Physics, Inc. v. Coherent Inc.*, 3 U.S.P.Q.2d 1737 (Fed. Cir. 1987).

Therefore, Grubb does not provide the necessary evidence for the Examiner to meet his burden of proving a *prima facie* case of lack of enablement of claims 14-18, 22-26, and 39-43. On the contrary, Grubb supports the enablement of Applicants' claimed methods. Accordingly, Applicants respectfully contend that the rejection of claims 14-18, 22-26, and 39-43 is improper and should be withdrawn.

Even if one were still not convinced that Grubb does not support the enablement rejection of the claimed methods, one must consider the evidence as a whole. Numerous other research articles have disclosed the aforementioned biological activities of didemnins and tamandarins. For example, Joullié and Li, "The Didemnins: Biological Properties, Chemistry and Total Synthesis," in *Studies in Natural Products Chemistry*, Vol. 10, Atta-ur-Rahman, Ed., Elsevier Science Publishers B.V., (1992), p. 241-302 ("Joullié") is a review of research relating to didemnins and similar compounds. Joullié was cited in Applicants' IDS dated June 28, 2001. In Section 2.2 of Joullié, subheading "Antitumor Activity," the antitumor properties of didemnins against a number of tumor cell lines and types are discussed. *Id.*, at 254-257. Like Grubb, Joullié also teaches that didemnins inhibit protein synthesis. *Id.*, at 254 ("The principle mode of action of the didemnins appear to be the inhibition of protein synthesis, although DNA and RNA syntheses are also affected.").

Another research article, Sakai, R., *et al.*, "Structure-Activity Relationships of the Didemnins," *J. Med. Chem. 39*:2819-2834 (1996) ("Sakai"), confirms the ability of

didemnins to inhibit protein synthesis. See Table 2, p. 2823, of Sakia. A copy of Sakai was cited in Applicants' IDS dated June 28, 2001.

Vervoot, H., and Fenical, W., "Tamandarins A and B: New Cytotoxic Depsipeptides from a Brazilian Ascidian of the Family Didemnidae," *J. Org. Chem.* *65*:782-792 (2000), likewise teaches that tamandarins A and B exhibit potent biological activities, include antiproliferative and antitumor activity, along with the ability to inhibit protein synthesis. A copy of this reference is included with the Supplemental IDS submitted herewith.

There are also several U.S. patents that are directed to didemnins and didemnin analogs and their use for methods of treatment. *See*, *e.g.*, U.S. Patent Nos. 4,950,649; 5,137,870; 6,034,058; and 6,156,724.

Thus, when considering all references cited herein, it is known to one of ordinary skill in the art that certain didemnins and tamandarins exert a range of biological properties, including inhibiting protein synthesis, cell growth, cell proliferation, and tumorigenesis, and of enhancing apoptosis. Furthermore, the Examiner has not provided any evidence that a person of skill in the art would doubt the statements and evidence of the cited references.

The Examiner also has the opinion that undue experimentation is required to practice the claimed invention. Applicants respectfully disagree. As noted above, a number of peer-reviewed scientific articles disclose didemnins and tamandarins. These articles also disclose methods of determining various assays for determining both the biological activities of these compounds and the relative potencies and efficacies. These

assays are well known in the art. Information that is well known in the art need not be included in the specification to satisfy 35 U.S.C. § 112, paragraph 1. Given the precise definition of the genus of claimed compounds, a person of skill in the art would be able to use these assays to practice the claimed methods without undue experimentation. *See In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). Accordingly, for at least these reasons, the specification of the present application provides an enabling disclosure for claims 14-18, 22-26, and 39-43.

The Examiner also cited Pfizenmayer *et al.*, *Bioorg. Med. Chem. Lett.* 8:3653-3656 (1998) ("Pfizenmayer") to support the enablement rejection. With respect to Pfizenmayer, the Examiner stated that

> [Pfizenmayer] on page 3653 states that didemnin B[,] which is one of the most potent natural members of the didemnin family, has shown antiviral, antitumor, and immunosuppressant activities is found to display some side effects such as hepatic toxicity and neuromuscular toxicity. Also, didemnin B was shown to be very cytotoxic to lymphocytes. Further, Applicant acknowledges on page 2, lines 14-20 in the instant specification by stating that despite the potency of didemnin B in isolated studies, its clinical effectiveness is hampered by the side effects associated with therapeutic doses of the compound. As with many anti-proliferative agents, didemnin B exhibits a relatively narrow therapeutic window. Although[] didemnin M and dehydrodidemnin B exhibit improved therapeutic potential, relative to didemnin B, a need still exists for anti-proliferative agents, which exhibit less toxicity at a therapeutic dose (i.e., didemnin analogs having a greater therapeutic index).

(Office Action, p. 7). The Examiner's position appears to require that the claimed methods meet a clinical effectiveness or to have a greater therapeutic index compared to prior art didemnins and tamandarins. Applicants respectfully assert that 35 U.S.C. § 112, paragraph 1, does not mandate such a requirement of the claimed method.

The enablement of a claim must be considered in light of what is being claimed and without importing unclaimed limitations. *See CFTM, Inc., v. Yieldup Int'l Corp.*, 68 U.S.P.Q.2d 1940, 1944 (Fed. Cir. 2003). Unless recited as a limitation, a claim to a product or method does not have to be commercially viable. *Id.* ("Enablement does not require an inventor to meet lofty standards for success in the commercial marketplace. Title 35 does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect."). Furthermore, the claimed method does not have to be safe enough to be approvable by the Food and Drug Administration. *See Brana*, 34 U.S.P.Q.2d at 1442 ("The stage at which an invention in [the pharmaceutical] field becomes useful is well before it is ready to be administered to humans."); *In re Hartop*, 135 U.S.P.Q. 419 (C.C.P.A. 1962) (recognizing that the FDA, and not the Patent Office, is responsible for determining safety and efficacy in humans).

The method claims presently rejected for lack of enablement do not contain any limitation relating to efficacy, safety, or therapeutic index. The claimed methods merely require that the applied composition, *e.g.*, the didemnin analog of Figure 1, exert the biological activity recited in the claim, *e.g.*, protein inhibition. It is well recognized that antineoplastic and immunosuppresive compounds may have significant side effects; however, this fact does not mean a claim to the use of such a compound is not enabled, as can be seen from the frequent patenting of methods of treatment using such compounds. In fact, several issued U.S. patents claim the use of didemnin analogs. *See*, *e.g.*, U.S. Patent Nos. 4,950,649; 5,137,870; 6,034,058; and 6,156,724.

For at least the reasons detailed above, the Examiner has not established a *prima facie* case of nonenablement of claims 14-18, 22-26, and 39-43. Furthermore, at least the reasons detailed above, the specification of the present application provides an enabling disclosure for claims 14-18, 22-26, and 39-43. Accordingly, Applicants respectfully request that the rejection of claims 14-18, 22-26, and 39-43 under 35 U.S.C. § 112, paragraph 1, be reconsidered and withdrawn.

Rejections under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 1-55 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point and distinctly claim the subject matter of the invention. Applicants respectfully traverse.

First, the Examiner has rejected claims 1, 19, and 27 because the claims recite "either." Applicants respectfully disagree with the Examiner. The test of whether a claim is indefinite is whether one of ordinary skill in the art would understand what is claimed when the claim is read in light of the specification. *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 1 U.S.P.Q.2d 1081, 1088 (Fed. Cir. 1986). Clearly, one of ordinary skill in the art would understand what is being claimed. The Examiner himself clearly understands what is being claimed and indeed has suggested claim language deemed to have better clarity. The Manual of Patent Examining Procedure ("MPEP") instructs on such a situation.

> [I]f the language used by applicant satisfies the statutory requirements of 35 U.S.C. 112, second paragraph, but the examiner merely wants the applicant to improve the clarity or precision of the language used, the claim must not be rejected under 35 U.S.C. 112, second paragraph, rather, the examiner should suggest improved language to the applicant.

MPEP § 2173.02, p. 2100-206, Original 8th Ed., August, 2001, May 2004 Revision.

While Applicants do not agree with the Examiner that the claims are indefinite, Applicants have amended the claims as suggested by the Examiner solely to further prosecution. The definition of R^2 and R^3 in claims 1, 19, and 27 have been amended. The amendments to these claims do not narrow the definitions of R^2 and R^3 and do not change the scope of the claims. The amendments deal solely with the form of the claim.

Second, the Examiner has rejected claims 5, 6, 31, and 32 because the claims refer to compound numbers. For example, claim 5 refers to compound 201. Applicants respectfully disagree that such reference to compound numbers is unclear. Again, Applicants contend that one of ordinary skill in the art would readily comprehend the scope and meaning of such claims when read in light of the specification. *Orthokinetics,* 1 U.S.P.Q.2d at 1088. The Examiner clearly understands to which structures the compound numbers refer. Thus, the rejection of claims 5, 6, 31, and 32 is improper.

However, in order to advance prosecution, Applicants have amended claims 5, 6, 31, and 32 to include the structure of the compounds in addition to the compound number. The amendments to these claims do not narrow the meaning of the compounds and do not change the scope of the claims. The amendments deal solely with the form of the claim.

Third, the Examiner has rejected claim 34 because the claim does not end with a period. Applicants thank the Examiner for identifying this typographical error. Claim 34 has been amended so that the claim ends with a period. This non-narrowing amendment deals solely with form and does not change the scope of the claim.

Fourth, the Examiner has rejected claims 44-55 for being improper Jepson claims. Applicants have amended claims 44-55. The subject matter of the amended claims is directed to methods of making the compounds of the invention. Support for the claims can be found throughout the application and in the Figures 3-6. No new matter has been added.

For at least the reasons and amendments detailed above, each of the rejections of claims 1-55 under 35 U.S.C. § 112, second paragraph, have been accommodated, traversed, or rendered moot. Accordingly, Applicants respectfully request that the rejection of claims 1-55 under 35 U.S.C. § 112, paragraph 2, be reconsidered and withdrawn.

Other Matters

Applicants request that the Examiner revise the Attorney Docket No. associated with the present application to be consistent with docket number of Applicants' current representative. The docket number of Applicants' current representative is 1694.0640001.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all currently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

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